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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
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EXAMINER	
FORMAN, B	
ART UNIT	**PAPER NUMBER**
1655	6

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/394,230	GUNDERSON ET AL.	
	Examiner	Art Unit	
	BJ Forman	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☒ Responsive to communication(s) filed on *13 September 1999* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

14) ☒ Notice of References Cited (PTO-892)
15) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
16) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
17) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
18) ☐ Notice of Informal Patent Application (PTO-152)
19) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-25 are indefinite in the recitations "substantially identical" and "substantially complete" because "substantially" is an indefinite quantitative term and therefore the quantity of identity or completeness is undefined. It is suggested that the claims be amended to delete "substantially".

b. Claims 19-25 are indefinite in step (c) because "determining the hybridization pattern" is a *non sequitur* to the preamble of Claim 19 i.e. "distinguishing individual polynucleotides". It is suggested that the claims be amended in step (c) to recite a method step for distinguishing individual polynucleotides.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cantor et al. (U.S. Patent No. 5,795,714, 18 August 1998) in view of Southern et al. (Genomics, 1992, 13:1008-1017).

Regarding Claim 1, Cantor et al. teach a method of determining the presence of a mutation in a target polynucleotide (Example 5) comprising the steps of providing a polynucleotide probe array (Example 5, line 18) wherein each probe comprises a double stranded region and a single stranded n-mer overhang region (Column 9, lines 51-56) such that the over hangs in each array constitute a complete set of n-mers (Column 8, lines 31-36); hybridizing a target polynucleotide to said overhangs in the array to generate a target hybridization pattern (Column 16, lines 34-36); and determining the presence of a mutation in the target polynucleotide by analyzing hybridization patterns (Column 8, lines 55-60, Example 5, Table 2, Table 3 and Fig. 13). Cantor et al. teach the method for detecting mutations and comparative sequencing. Cantor et al. do not teach providing at least two identical polynucleotide probe arrays wherein the target polynucleotide is hybridized to one array and a reference polynucleotide is hybridized to a second array and wherein the presence of a mutation is determined by comparing the target and reference hybridization patterns. However, Southern et al. teach a method for analyzing and comparing nucleic acid sequences by hybridization to arrays wherein the analysis and comparison of hybridization patterns determines the presence of a mutation (page 1008, right column, third paragraph, lines 9-11 and page 1013, Table 2). To teach the method, Southern et al. analyze and compare hybridization patters of two known nucleic acid sequences. Southern et al. do not refer to the nucleic acid sequences as target and reference sequences however, it would have been obvious to one of ordinary skill in the art to refer to the Sequence I and Sequence II taught by Southern et al. as target and reference sequences. Additionally, Southern et al. teach the method would be applicable in the analysis and comparisons of gene sequences which are known to be

affected by mutations e.g. p53 and CFTR (page 1015, left column, second paragraph, lines 13-23) and it would have been obvious to one of ordinary skill in the art that the analysis and comparisons to identify the mutations taught by Southern would involve the analysis and comparisons between target and reference sequences.

Regarding Claim 2, Cantor et al. teach the hybridized polynucleotide is ligated to the probe (Column 9, lines 52-58 and Example 5, lines 18-22).

Regarding Claim 3, Cantor et al. teach the hybridized polynucleotide is ligated to the probe (Example 5, lines 28-30). Cantor et al. do not discuss the reference polynucleotide. However, reference polynucleotides were known to one of ordinary skill in the art as discussed above and the skilled practitioner would have known that for comparison purposes, a target and reference polynucleotide would be treated under equal conditions i.e. ligated to the probe.

Regarding Claim 4, Cantor et al. teach the overhangs have free 5' ends (Example 2, Column 19, lines 53-54).

Regarding Claim 5, Cantor et al. teach the overhangs have free 3' ends (Example 2, Column 19, lines 18-19).

Regarding Claim 6, Cantor et al. teach the n-mer comprises from about 4 to 50 nucleotides (Column 7, lines 25-31).

Regarding Claim 7, Cantor et al. teach the mutation is a substitution mutation i.e. mismatch (Column 23, lines 1-5 and Tables 2 & 3).

Regarding Claims 8 and 9, Cantor et al. teach the method wherein the mutations comprise genetic variation, single nucleotide mutations, heterologous nucleic acid sequences and inherited mutations which cause disease (Column 15, lines 56-67 and Column 16, lines 21-23). One skilled in the art would have known that the above mutations include deletion mutations and insertion mutations

Regarding Claim 10, Cantor et al teach the method wherein specific polynucleotides are analyzed as diagnostic tools in the identification of family genetic variation and inherited mutation which cause disease (Column 15, lines 56-67). The skilled practitioner would have known that inherited mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene and the p53 gene cause disease and that the method of Cantor et al. and Southern et a. would be used to determine the presence of a mutation in the CFTR and p53 genes as taught by Southern et al. (page 1015, left column, middle paragraph, last 5 lines).

Regarding Claim 11, Cantor et al. does not discuss arrays are arranged in parallel. However, Southern et al. teaches arrays arranged in parallel (page 1011, Fig. 3 figure legend). Specifically, Southern et al. teach the array having 4 copies of all possible octapurines is hybridized with Sequence I (Fig3. left panel); analyzed by imaging, quantitation, and normalization (page 1011, left column middle paragraph); and compared to the hybridization pattern for Sequence II (Fig. 3 figure legend, last two lines, figure not shown).

It would have been ***prima facie*** obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Cantor et al. with the teachings of Southern et al. to obtain the claimed invention because the skilled practitioner in the art would have been motivated with a reasonable expectation of success to modify the Cantor et al method of analyzing hybridization patterns to determine the presence of a mutation with the Southern et al. method for analyzing and comparing hybridization patterns of nucleic acid sequences to determine the presence of a mutation for the expected benefit of rapid mutation analysis e.g. the ability to detect single base differences between sequences of several hundred in length i.e. CFTR and p53 gene sequences as taught by Southern et al. (page 1015, left column, middle paragraph). Additionally, it would have been obvious to the skilled practitioner to apply the Southern et al. hybridization arrays arranged in parallel to the Cantor et al. method of hybridization analysis because the skilled practitioner would have been motivated

with a reasonable expectation of success to analyze hybridization patterns wherein the hybridization arrays are arranged in parallel for the expected benefit of emphasizing the differences between the two patterns resulting in rapid mutation analysis as taught by Southern et al. (page 1014, left column, third paragraph).

5. Regarding Claim 12, Cantor et al. teach a method of determining whether two or more polynucleotides are identical (Example 13) comprising the steps of providing a polynucleotide probe array wherein each probe comprises a double stranded region and a single stranded n-mer overhang region (Column 9, lines 51-56) such that the over hangs in each array constitute a complete set of n-mers (Column 8, lines 31-36); hybridizing a first polynucleotide to said overhangs in the array to generate a first hybridization pattern (Example 13, Column 30, lines 52-65); hybridizing a second target polynucleotide to said overhangs in the array to generate a second hybridization pattern (Column 31, lines 1-6); and determining whether the polynucleotides are identical by analyzing the hybridization patterns (Column 31, lines 4-7). Cantor et al. teach the method wherein both first and second polynucleotides are hybridized to the same array. Cantor et al. do not teach the providing at least two identical polynucleotide probe arrays wherein the first polynucleotide is hybridized to one array and the second polynucleotide is hybridized to the second array however hybridization of polynucleotides to identical probe arrays were known in the are as taught by Southern et al. Southern et al. teach a method for determining whether two or more polynucleotides are identical wherein a first polynucleotide is hybridized to one array and a second polynucleotide is hybridized to a second array to generate a first and second hybridization pattern and wherein the comparison between the hybridization patterns determine whether the polynucleotides are identical (page 1011, Fig. 3 figure legend and page 1013, Table 2).

Regarding Claim 13, Cantor et al. teach the hybridized target polynucleotide is ligated to the probe (Column 9, lines 52-58 and Example 5, lines 18-22).

Regarding Claim 14, Cantor et al. teach the hybridized polynucleotide is ligated to the probe (Example 5, lines 28-30). Cantor et al. do not discuss a reference polynucleotide. However, reference polynucleotides were known to one of ordinary skill in the art and the skilled practitioner would have known that for comparison purposes, a target and reference polynucleotide would be treated under equal conditions i.e. ligated to the probe.

Regarding Claim 15, Cantor et al. teach the overhangs have free 5' ends (Example 2, Column 19, lines 53-54).

Regarding Claim 16, Cantor et al. teach the overhangs have free 3' ends (Example 2, Column 19, lines 18-19).

Regarding Claim 17, Cantor et al. teach the n-mer comprises from about 4 to 50 nucleotides (Column 7, lines 25-31).

Regarding Claim 18, Cantor et al. does not discuss arrays are arranged in parallel. However, Southern et al. teaches arrays arranged in parallel (page 1011, Fig. 3 figure legend). Specifically, Southern et al. teach the array having 4 copies of all possible octapurines is hybridized with Sequence I (Fig3. left panel); analyzed by imaging, quantitation, and normalization (page 1011, left column middle paragraph); and compared to the hybridization pattern for Sequence II (Fig. 3 figure legend, last two lines, figure not shown).

It would have been ***prima facie*** obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Cantor et al. with the teachings of Southern et al. to obtain the claimed invention because the skilled practitioner in the art would have been motivated with a reasonable expectation of success to modify the Cantor et al method of analyzing hybridization patterns of first and second polynucleotide with the Southern et al. method wherein a first and second hybridization pattern are analyzed and

compared to determine whether the polynucleotides are identical for the expected benefit of rapid mutation analysis e.g. the ability to detect single base differences between sequences of several hundred in length as taught by Southern et al. (page 1015, left column, middle paragraph). Additionally, it would have been obvious to the skilled practitioner to apply the Southern et al. hybridization arrays arranged in parallel to the Cantor et al. method of hybridization analysis because the skilled practitioner would have been motivated with a reasonable expectation of success to analyze hybridization patterns wherein the hybridization arrays are arranged in parallel for the expected benefit of emphasizing the differences between the two patterns resulting in rapid mutation analysis as taught by Southern et al. (page 1014, left column, third paragraph).

6. Regarding Claim 19, Cantor et al. teach a method of distinguishing individual polynucleotides in a mixture of polynucleotides (Column 4, line 24) comprising the steps of providing a polynucleotide probe array wherein each probe comprises a double stranded region and a single stranded n-mer overhang region (Column 9, lines 51-56) such that the over hangs in each array constitute a complete set of n-mers (Column 8, lines 31-36); hybridizing the polynucleotides in the mixture to said overhangs of probe polynucleotides in the array (Column 9, lines 56-58); and determining the hybridization pattern (Column 8, lines 55-60). Cantor et al. do not discuss providing at least two identical polynucleotide arrays. However, multiple identical polynucleotide arrays were known to one of skill in the art as taught by Southern et al. (page 1010, left column, last two paragraphs page 1011, Fig. 3)

Regarding Claim 20, Cantor et al. teach the method further comprising enumerating the distinguished individual polynucleotides (Column 9, lines 43-50).

Regarding Claim 21, Cantor et al. teach the target polynucleotide is ligated to the probe (Column 9, lines 55-65).

Regarding Claim 22, Cantor et al. teach the overhangs have free 5' ends (Example 2, Column 19, lines 53-54).

Regarding Claim 23, Cantor et al. teach the overhangs have free 3' ends (Example 2, Column 19, lines 18-19).

Regarding Claim 24, Cantor et al. teach the n-mer comprises from about 4 to 50 nucleotides (Column 7, lines 25-31).

Regarding Claim 25, Cantor et al. does not discuss arrays are arranged in parallel. However, Southern et al. teaches arrays arranged in parallel (page 1011, Fig. 3 figure legend). Specifically, Southern et al. teach the array having 4 copies of all possible octapurines is hybridized with Sequence I (Fig3. left panel); analyzed by imaging, quantitation, and normalization (page 1011, left column middle paragraph); and compared to the hybridization pattern for Sequence II (Fig. 3 figure legend, last two lines, figure not shown).

It would have been ***prima facie*** obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Cantor et al. with the teachings of Southern et al. to obtain the claimed invention because the skilled practitioner in the art would have been motivated with a reasonable expectation of success to modify the Cantor et al method of distinguishing individual polynucleotides with the Southern et al. method wherein at hybridization patterns from at least two identical polynucleotide arrays are compared to distinguish individual polynucleotides in a mixture for the expected benefit of rapid analysis and the ability to detect single base differences between sequences of several hundred in length as taught by Southern et al. (page 1015, left column, middle paragraph). Additionally, it would have been obvious to the skilled practitioner to apply the Southern et al. hybridization arrays arranged in parallel to the Cantor et al. method of hybridization analysis because the skilled practitioner would have been motivated with a reasonable expectation of success to analyze hybridization patterns wherein the hybridization arrays are arranged in parallel for the

expected benefit of emphasizing the differences between the two patterns resulting in rapid mutation analysis as taught by Southern et al. (page 1014, left column, third paragraph).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (703) 306-5878. The examiner can normally be reached on 6:45 TO 4:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-8742 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

BJ Forman, Ph.D.
March 6, 2000

SUPERVISORY PATENT EXAMINER
PRIMARY EXAMINER